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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
BLANCHARD, DAVID J	

ART UNIT	PAPER NUMBER
1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/755,382	HANSEN ET AL.	
	Examiner	Art Unit	
	David J. Blanchard	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-61* is/are pending in the application.

4a) Of the above claim(s) *1-29 and 43-61* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 January 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/13/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of the invention of Group II, claims 30-42 in the reply filed on 13 February 2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 1-61 are pending.

3. Claims 1-29 and 43-61 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

4. Claims 30-42 are under examination.

Specification

5. The disclosure is objected to because of the following informalities:

a. The first line of the specification needs to be updated to reflect the current status of USSN 09/253,794, filed February 22, 1999, which is now U.S. Patent No. 6,676,924.

b. The first line of the specification needs to be updated to indicate that the instant application is a CIP of USSN 09/253,794, filed 2/22/1999 (see "Priority" section below).

c. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. Applicant

should restrict the title to the claimed diagnostic method using the humanized class III, anti-CEA monoclonal antibody.

Claim Objections

6. Claim 40 is objected to as reciting "light and heavy chain variable regions chains", which should be corrected to "light and heavy chain variable regions".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

8. Claims 30-42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 30-42 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. There is no detection step wherein the humanized class III, anti-CEA monoclonal antibody conjugate is quantitated or visualized nor any standard for comparing the measured level or detectable CEA in a patient for the diagnosis. Merely, administering said conjugate does not result in a method of diagnosing as required by the preamble of claim 30. Further, the preamble of claim 30 is ambiguous because it does not state what the claimed diagnostic method is intended to accomplish. Amending the

preamble of claim 30 to recite "A method of diagnosing cancer..." would clarify this ambiguity and provide a basis for the addition of a resolution step to the claim, which reads back on the preamble and results in "A method of diagnosing cancer in a patient...", for example.

While all of the technical details of a method need not be recited, the claims should include enough information to clearly and accurately describe the invention and how it is practiced. The method steps should at least include reagents necessary for the assay, a detection step in which the reaction products are quantitated or visualized and a correlation step describing how the results of the assay allows the determination of, for example, diagnosing cancer in a patient.

b. Claims 30-42 are indefinite in the recitation "a diagnostic agent bound to a humanized Class III, anti-CEA, monoclonal antibody" in claim 30 because it unclear what is contemplated by the phrase. Is the diagnostic agent conjugated or linked to the humanized antibody or does the humanized antibody bind the diagnostic agent and CEA, i.e., is the monoclonal antibody bispecific? As written, one of skill in the art would not be reasonably apprised of the metes and bounds of the claimed invention. Amending claim 30 to recite "a diagnostic agent conjugated to a humanized Class III, anti-CEA, monoclonal antibody" or similar language, provided no new matter is introduced would overcome this rejection.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 30-42 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of diagnosing cancer in a patient comprising administering a humanized anti-CEA monoclonal antibody or antigen-binding fragment thereof conjugated to a diagnostic agent, and quantitating or visualizing the humanized anti-CEA monoclonal antibody conjugate in said patient, wherein the humanized anti-CEA monoclonal antibody comprises a light chain variable region comprising CDRL1 comprising SEQ ID NO:20, CDRL2 comprising SEQ ID NO:21 and CDRL3 comprising SEQ ID NO:22 and a heavy chain variable region comprising CDRH1 comprising SEQ ID NO:23, CDRH2 comprising SEQ ID NO:24 and CDRH3 comprising SEQ ID NO:25, does not reasonably provide enablement for a method of diagnosing a patient comprising administering (i) a humanized anti-CEA monoclonal antibody or fragment thereof conjugated to a diagnostic agent wherein the humanized anti-CEA monoclonal antibody comprises only a CDR selected from the group consisting of SEQ ID Nos:20, 21, 22, 23, 24 and 25 and (ii) said method of diagnosing wherein the only active method step comprises administering a humanized anti-CEA monoclonal antibody conjugated to a diagnostic agent. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in In re Wands, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,
"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention is CEA-specific cancer immunodiagnosis and radioimmunodetection in a patient, and engineered or humanized antibodies specific for CEA, where the relative skill of those in the art is deemed to be high.

The claims are broadly drawn to a method of diagnosing a patient comprising administering a humanized anti-CEA monoclonal antibody bound to a diagnostic agent wherein said humanized anti-CEA monoclonal antibody comprises a CDR selected from the group consisting of SEQ ID Nos:20, 21, 22, 23, 24 and 25 and combinations thereof. Thus, the claims broadly encompass a method of diagnosing any disorder or disease in a patient, comprising administering a diagnostically labeled (i.e., interpretation of "a diagnostic agent bound to...") humanized Class III, anti-CEA monoclonal antibody or fragments thereof that do not contain all six CDRs, three from the heavy chain variable domain (VH) and three from the light chain variable domain (VL) and do not bind antigen or do not bind CEA, or administering a humanized Class III, anti-CEA monoclonal antibody that contains any combination of CDRs selected from SEQ

ID Nos:20-25 that do not bind antigen or do not bind CEA as well as a diagnostic method wherein the critical feature of detection or visualization of the administered humanized anti-CEA monoclonal antibody conjugate is not claimed.

The specification teaches only a method of diagnosing cancer in a patient comprising administering a radiolabelled humanized anti-CEA antibody that contains all six CDRs (i.e., SEQ ID Nos:20, 21, 22, 23, 24 and 25) from the heavy and light chains of a parental mouse anti-CEA monoclonal antibody (i.e., MN-14), wherein the humanized anti-CEA antibody retains the binding specificity of the parental mouse anti-CEA monoclonal antibody and the radioactivity is localized in tissues (see pp. 11-12 and Examples 8-11). The specification does not teach a diagnostic method wherein the only active method step is administration of a humanized anti-CEA monoclonal antibody conjugated to a diagnostic agent or wherein the administered humanized anti-CEA monoclonal antibody contains only one or just any combination of the CDRs of mouse monoclonal antibody MN-14, i.e., wherein the humanized antibody retains the binding specificity of parental monoclonal antibody, MN-14. There are no working examples of a humanized anti-CEA monoclonal antibody or fragment thereof that contains only one or just any combination of the CDRs selected from SEQ ID Nos:20, 21, 22, 23, 24 and 25, wherein the humanized antibody retains the CEA binding specificity of the parent antibody (i.e., MN-14) or a method of diagnosing a patient comprising administering said humanized anti-CEA monoclonal antibody bound to or conjugated to a diagnostic agent.

The state of the prior art is such that it is well established in the art that the formation of an intact antigen-binding site of antibodies typically requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs or hypervariable regions, which provide the majority of the contact residues for the binding of the antibody to its target epitope (Paul, Fundamental Immunology, 3rd Edition, 1993, pp. 292-295, under the heading "Fv Structure and Diversity in Three Dimensions"). The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity, which is characteristic of the immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites (Paul, page 293, first column, lines 3-8 and line 31 to column 2, line 9 and lines 27-30). Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc. Natl. Acad. Sci. USA, 79:1979-1983, 1982). Rudikoff et al teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. Coleman P. M. (Research in Immunology, 145:33-36, 1994) teaches that even a very conservative substitution may abolish binding or may have very little effect on the binding affinity (see pg. 35, top of left

column and pg. 33, right column). It is unlikely that humanized anti-CEA antibodies and fragments thereof that contain only one or any combination of CDRs selected from SEQ ID Nos:20, 21, 22, 23, 24 and 25, which contain less than the full complement of CDRs from the heavy and light chain variable regions of parental mouse monoclonal antibody MN-14 in their proper order and in the context of framework sequences, have the required CEA binding function. There is no guidance or direction provided by applicant to assist the skilled artisan in making and using humanized anti-CEA antibodies and fragments thereof comprising heavy and light chain variable domains that do not contain the full complement of CDRs, three from the light chain and three from the heavy chain of parental mouse monoclonal antibody MN-14 that bind CEA. Further, a fragment of a humanized anti-CEA monoclonal antibody (i.e., "fragment thereof") that contains only one or just any combination of CDRs selected from SEQ ID Nos:20, 21, 22, 23, 24 and 25 reads on just the light chain variable domain or the heavy chain variable domain as well as any fragments thereof including a single CDR or a single framework region or a CDR-FR fragment. One of skill in the art would neither expect nor predict the appropriate functioning of the humanized anti-CEA antibody and fragments thereof as broadly as is claimed. Additionally, the claimed diagnostic method lacks a step in which the administered humanized anti-CEA monoclonal antibody is quantitated or visualized, which is a critical feature of the claimed diagnostic method (e.g., see Example 11 at pg. 29 of the specification). A feature, which is taught as critical in a specification and is not recited in the claims should result in a rejection of such claim under the

enablement provision section of 35 U.S.C. 112. See *In re Mayhew*, 527 F.2d 1229, 1233, 188 USPQ 356, 358 (CCPA 1976). See MPEP 2164.08(c).

In view of the lack of the predictability of the art to which the invention pertains as evidenced by Paul, W. E., Rudikoff et al and Coleman P.M., the lack of guidance and direction provided by applicant, and the absence of working examples, undue experimentation would be required to practice the claimed diagnostic method comprising administering a humanized anti-CEA monoclonal antibody conjugate that contains only one or just any combination of CDRs selected from SEQ ID Nos:20, 21, 22, 23, 24 and 25 with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed diagnostic method using a humanized anti-CEA monoclonal antibody conjugate that contains only one or just any combination of CDRs selected from SEQ ID Nos:20, 21, 22, 23, 24 and 25 and absent working examples providing evidence which is reasonably predictive that the claimed humanized anti-CEA monoclonal antibody conjugate binds CEA, commensurate in scope with the claimed invention.

Priority

11. The filing date of instant claims 30-39 and 41-42 is deemed to be the filing date of parent application USSN 08/318,157, i.e., 10/5/1994. The filing date of originally filed claim 40 is deemed to be that of the instant application, i.e., 1/13/2004. The parent applications, USSNs 09/253,794 and 08/318,157 do not provide adequate written support for the limitation wherein each of the light and

heavy chain variable regions comprise FRs from at least two human antibodies, which is an originally filed claim limitation in the present application. If applicant desires priority prior to 1/13/2004; applicant is invited to point out and provide documentary support for the priority of instant claim 40. Applicant is reminded that such priority for the instant limitations requires written description and enablement under 35 U.S.C. § 112, first paragraph.

12. This application repeats a substantial portion of prior Application Nos. 09/253,794, filed 2/22/1999 and 08/318,157, filed 10/5/1994, and adds and claims additional disclosure not presented in the prior application as discussed above. Since this application names an inventor or inventors named in the prior application, it may constitute a continuation-in-part of the prior application. Should applicant desire to obtain the benefit of the filing date of the prior application, attention is directed to 35 U.S.C. 120 and 37 CFR 1.78.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 30-39 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hansen et al (Cancer, 71(11):3478-3485, June 1, 1993) as evidenced by the specification in view of Robinson et al (U.S. Patent 5,618,920, issued 4/8/1997) and Adair et al (WO 92/01059, published 1/23/1992, IDS reference 7 filed 3/13/06).

Claims 30-39 and 41 are being interpreted as drawn to a method of diagnosing a patient with a colon cancer comprising administering a humanized Class III, anti-CEA monoclonal antibody or fragment thereof conjugated to a radionuclide (i.e., diagnostic agent), detection or localization of the radioactivity, wherein said humanized antibody comprises a light chain variable region

comprising CDRL1 comprising SEQ ID NO:20, CDRL2 comprising SEQ ID NO:21 and CDRL3 comprising SEQ ID NO:22 and a heavy chain variable region comprising CDRH1 comprising SEQ ID NO:23, CDRH2 comprising SEQ ID NO:24 and CDRH3 comprising SEQ ID NO:25 and human framework regions (FRs) including human REI light chain FRs (i.e., SEQ ID Nos:26-29) and human KOL FRs (i.e., includes SEQ ID Nos:33 and 39), wherein said humanized Class III, anti-CEA monoclonal antibody is unreactive with meconium antigen by enzyme immunoassay and retains the binding specificity of a parental murine Class III, anti-CEA monoclonal antibody.

Hansen et al teach the hybridoma that produces monoclonal antibody MN-14, which is a Class III anti-CEA monoclonal antibody, being unreactive with meconium by enzyme immunoassay (see Table 1) and ^{131}I-MN-14 demonstrated superior tumor targeting in a human xenograft model and consistently stronger staining of frozen sections and showed excellent specificity and sensitivity in a phase I clinical study to detect CEA-containing tumors by radioimmunodetection (see entire document, particularly pp. 3479, 3481-2484, Figs. 2-3). As evidenced by the specification the light chain CDR sequences of SEQ ID Nos:20-22 and the heavy chain CDR sequences of SEQ ID Nos:23-25 are the MN-14 monoclonal antibody CDR sequences and necessarily present in the MN-14 monoclonal antibody of Hansen et al (see specification at pg. 8 and Fig. 5A-B). Hansen et al do not specifically teach a method for diagnosing colon cancer in a human patient comprising administering a ^{131}I-humanized Class III, anti-CEA monoclonal antibody or antigen-binding fragment thereof comprising the recited light and

heavy chain MN-14 CDR sequences of SEQ ID Nos:20-25 that retains the binding specificity of the parental murine MN-14 Class III, anti-CEA monoclonal antibody and comprising human FRs, including the light chain REI human FRs (i.e., SEQ ID NO:26-29) and the heavy chain KOL human FRs (i.e., includes SEQ ID Nos:33 and 39). These deficiencies are made up for in the teachings of Robinson et al and Adair et al.

Robinson et al teach Fv derived from a known antibody (see columns 12-22). Robinson et al teach Fv, determination of nucleic acids encoding VH and VL of any known antibody and use of said VH and VL to produce Fv (see column 1-45, and columns 12-22). Robinson et al teach that "The invention also produces consensus sequences and specific oligonucleotide sequences useful as probes for hybridization and priming cDNA synthesis of any hybridoma mRNA coding for variable regions of any desired specificity." (see column 4, last paragraph).

Adair et al teach CEA-specific humanized antibodies and antigen-binding fragments thereof (i.e., Fab, Fab', F(ab')2, scFv) that are less immunogenic in human patients compared to mouse antibodies and thus, better suited for human therapy (see pp. 2, 5-6). Adair et al teach determination of the CDR residues and the use of conventional human FRs, including REI for the light chain and KOL for the heavy chain for humanization and according to Adair, methods of obtaining the DNA sequences from a hybridoma cell line encoding a particular monoclonal antibody are well known in the art (see entire document, particularly pp. 7, 9 (last five lines) and 11-12).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a method of diagnosing colon cancer in a human patient comprising administering an ^{131}I-humanized Class III, anti-CEA monoclonal antibody or fragment thereof, detection or localization of the radioactivity, wherein the humanized antibody comprises the MN-14 CDR sequences of SEQ ID Nos:20-25, the human REI light chain FRs and the human KOL heavy chain FRs, retains the binding specificity of parental antibody MN-14 and is unreactive with meconium by enzyme immunoassay.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to have produced a method of diagnosing colon cancer in a human patient comprising administering an ^{131}I-humanized Class III, anti-CEA monoclonal antibody or fragment thereof, detection or localization of the radioactivity, wherein the humanized antibody comprises the MN-14 CDR sequences of SEQ ID Nos:20-25, the human REI light chain FRs and the human KOL heavy chain FRs, retains the binding specificity of parental antibody MN-14 and is unreactive with meconium by enzyme immunoassay in view of Hansen et al as evidenced by the specification and Robinson et al and Adair et al because Hansen et al teach the hybridoma that produces monoclonal antibody MN-14, which is a Class III anti-CEA monoclonal antibody, being unreactive with meconium by enzyme immunoassay and necessarily comprises the light chain CDRs of SEQ ID Nos:20-22 and heavy chain CDRs of SEQ ID Nos:23-25 as evidenced by the

specification and ^{131}I-MN-14 demonstrated excellent specificity and sensitivity in a phase I clinical study to detect CEA-containing tumors by radioimmunodetection and Robinson et al teach determination of nucleic acids encoding VH and VL of any known antibody as well as consensus sequences and specific oligonucleotide sequences useful as probes for hybridization and priming cDNA synthesis of any hybridoma mRNA coding for variable regions of any desired specificity and Adair et al teach CEA-specific humanized antibodies and antigen-binding fragments thereof (i.e., Fab, Fab', F(ab')2, scFv) that are less immunogenic in human patients compared to mouse antibodies, determination of the CDRs, the use of human REI FRs for the light chain and human KOL FRs for the heavy chain. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to apply the method of Robinson et al to obtain the nucleic acids encoding the VH and VL of the art known MN-14 monoclonal antibody from the MN-14 hybridoma of Hansen et al, and humanize the MN-14 monoclonal antibody using the human REI light chain FRs (i.e., SEQ ID Nos:26-29) and the human KOL heavy chain FRs (i.e., includes SEQ ID Nos:33 and 39) for radioimmunodetection of colon cancer in human patients in view that ^{131}I-MN-14 demonstrated excellent specificity and sensitivity in a phase I clinical study to detect CEA-containing tumors by radioimmunodetection as taught by Hansen et al. The motivation to make the above modifications to produce a ^{131}I-humanized Class III, anti-CEA monoclonal antibody for diagnosing colon cancer in human patients by radioimmunodetection is made explicit in the teachings of Adair et al, which indicate that humanized

antibodies are less immunogenic in human patients compared to mouse antibodies. Thus, there would be an advantage of using a ^{131}I-humanized Class III, anti-CEA monoclonal antibody that retains the binding specificity (CEA) of the parental mouse MN-14 antibody and is unreactive with meconium antigen (i.e., specific for CEA) for diagnosing colon cancer in human patients. Further, Robinson et al state "The invention also produces consensus sequences and specific oligonucleotide sequences useful as probes for hybridization and priming cDNA synthesis of any hybridoma mRNA coding for variable regions of any desired specificity." (see column 4, last paragraph). Thus, the art recognized that there was a reasonable expectation of success that the nucleic acid sequence of the VH and VL of the art known MN-14 antibody could be established from the MN-14 hybridoma using techniques disclosed in the references used in the instant rejection. Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have produced a method of diagnosing colon cancer in a human patient comprising administering an ^{131}I-humanized Class III, anti-CEA monoclonal antibody or fragment thereof, detection or localization of the radioactivity, wherein the humanized antibody comprises the MN-14 CDR sequences of SEQ ID Nos:20-25, the human REI light chain FRs and the human KOL heavy chain FRs, retains the binding specificity of parental antibody MN-14 and is unreactive with meconium by enzyme immunoassay in view of Hansen et al as evidenced by the specification and Robinson et al and Adair et al.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

15. Claim 40 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hansen et al (Cancer, 71(11):3478-3485, June 1, 1993) as evidenced by the specification in view of Robinson et al (U.S. Patent 5,618,920, issued 4/8/1997) and Leung et al (US 2003/0040606 A1, filed 6/27/2001).

Claim 40 is interpreted as being drawn to a method of diagnosing a patient with colon cancer comprising administering a humanized Class III, anti-CEA monoclonal antibody or fragment thereof conjugated to a radionuclide (i.e., diagnostic agent), detection or localization of the radioactivity (i.e., radioimmunodetection), wherein said humanized antibody comprises a light chain variable region comprising CDRL1 comprising SEQ ID NO:20, CDRL2 comprising SEQ ID NO:21 and CDRL3 comprising SEQ ID NO:22 and a heavy chain variable region comprising CDRH1 comprising SEQ ID NO:23, CDRH2 comprising SEQ ID NO:24 and CDRH3 comprising SEQ ID NO:25 and each of said light and heavy chain variable regions comprise frameworks (FRs) from at least two human antibodies and said humanized antibody is unreactive with meconium antigen by enzyme immunoassay.

Hansen et al as evidenced by the specification have been described supra. Hansen et al do not specifically teach a method for diagnosing colon cancer in a patient comprising administering and detecting a humanized Class III,

anti-CEA monoclonal antibody or antigen-binding fragment thereof conjugated to a radionuclide and comprising the light and heavy chain MN-14 CDR sequences of SEQ ID Nos:20-25 and wherein each of the light and heavy chain variable regions of the humanized antibody comprise FRs from at least two human antibodies. These deficiencies are made up for in the teachings of Robinson et al and Leung.

Robinson et al have been described supra.

Leung teaches a method antibody humanization referred to as "framework (FR) patching" wherein each FR sequence (i.e., FR1, FR2, FR3 and FR4) of a mouse antibody are replaced or "patched" with the corresponding human FR sequence from different human antibodies having the highest degree of homology to the corresponding mouse FR, wherein the humanized antibody has reduced immunogenicity in human patients compared to the mouse antibody and hence, is better suited for human therapy and the methodology of Leung provides flexibility in the choice of FR sequences, increasing the chance of success in maintaining the specificity and affinity of the parental mouse antibody and minimizes the need to reintroduce framework amino acids derived from the parental mouse antibody (see entire document, particularly pp. 3-5 and abstract).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a method of diagnosing colon cancer in a human patient comprising administering an ^{131}I-humanized Class III, anti-CEA monoclonal antibody or fragment thereof, detection or localization of the radioactivity, wherein the light and heavy chain

variable regions of the humanized antibody comprise the MN-14 CDR sequences of SEQ ID Nos:20-25 and each of the light and heavy chain variable regions comprise FRs from at least two human antibodies and the humanized antibody is unreactive with meconium by enzyme immunoassay.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to have produced a method of diagnosing colon cancer in a human patient comprising administering an ^{131}I-humanized Class III, anti-CEA monoclonal antibody or fragment thereof, detection or localization of the radioactivity, wherein the light and heavy chain variable regions of the humanized antibody comprise the MN-14 CDR sequences of SEQ ID Nos:20-25 and each of the light and heavy chain variable regions comprises FRs from at least two human antibodies and the humanized antibody is unreactive with meconium by enzyme immunoassay in view of Hansen et al as evidenced by the specification and Robinson et al and Leung because Hansen et al teach the hybridoma that produces monoclonal antibody MN-14, which is a Class III anti-CEA monoclonal antibody, being unreactive with meconium by enzyme immunoassay (i.e., specific for CEA) and necessarily comprises the light chain CDRs of SEQ ID Nos:20-22 and heavy chain CDRs of SEQ ID Nos:23-25 as evidenced by the specification and ^{131}I-MN-14 demonstrated excellent specificity and sensitivity in a phase I clinical study to detect CEA-containing tumors by radioimmunodetection and Robinson et al teach determination of nucleic acids encoding VH and VL of any known antibody as well as consensus sequences and specific oligonucleotide sequences useful

as probes for hybridization and priming cDNA synthesis of any hybridoma mRNA coding for variable regions of any desired specificity and Leung teach antibody humanization wherein each FR sequence (i.e., FR1, FR2, FR3 and FR4) of a mouse antibody are replaced or "patched" (i.e., FR patching) with the most homologous corresponding human FR sequence from different human antibodies, wherein the humanized antibody has reduced immunogenicity in human patients compared to the mouse antibody and hence, is better suited for human therapy. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated by the goal of reducing the immunogenicity of mouse monoclonal antibody MN-14 for radioimmunodetection in human colon cancer patients, to apply the method of Robinson et al to obtain the nucleic acids encoding the VH and VL of the art known MN-14 monoclonal antibody from the MN-14 hybridoma of Hansen et al, and humanize the MN-14 monoclonal antibody according to the FR patching method of Leung, which separately selects the most homologous corresponding human FR sequences from different human antibodies, providing flexibility in the choice of FR sequences, increasing the chance of success in maintaining the specificity and affinity of the original antibody, MN-14, and minimizes the need to reintroduce framework amino acids derived from parental mouse monoclonal antibody, MN-14. Thus, there would be an advantage to using a ^{131}I-humanized Class III, anti-CEA monoclonal antibody that retains the binding specificity and affinity of the parental mouse MN-14 antibody and is unreactive with meconium antigen (i.e., specific for CEA) for diagnosing colon cancer in human patients. Further,

Robinson et al state "The invention also produces consensus sequences and specific oligonucleotide sequences useful as probes for hybridization and priming cDNA synthesis of any hybridoma mRNA coding for variable regions of any desired specificity." (see column 4, last paragraph). Thus, the art recognized that there was a reasonable expectation of success that the nucleic acid sequence of the VH and VL of the art known MN-14 antibody could be established from the MN-14 hybridoma using techniques disclosed in the references used in the instant rejection. Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have produced a method of diagnosing colon cancer in a human patient comprising administering an ^{131}I-humanized Class III, anti-CEA monoclonal antibody or fragment thereof, detection or localization of the radioactivity, wherein the light and heavy chain variable regions of the humanized antibody comprise the MN-14 CDR sequences of SEQ ID Nos:20-25 and each of the light and heavy chain variable regions comprises FRs from at least two human antibodies and the humanized antibody is unreactive with meconium by enzyme immunoassay in view of Hansen et al as evidenced by the specification and Robinson et al and Leung.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Double Patenting

16. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude"

granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

17. Claims 30-42 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 14-18 and 20 of U.S. Patent No. 6,676,924. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are drawn to a method of diagnosing a patient or a patient with a CEA-producing cancer selected from colon, breast and lung cancer comprising administering a conjugate comprising a humanized Class III, anti-CEA monoclonal antibody or fragment thereof bound to a diagnostic agent wherein the humanized Class III, anti-CEA monoclonal antibody or fragment thereof comprises a CDR selected from SEQ ID Nos:20, 21, 22, 23, 24 and 25, and a combination thereof, wherein said humanized Class III, anti-CEA monoclonal antibody is unreactive with meconium antigen by enzyme immunoassay and retains the binding specificity of

a parental murine Class III, anti-CEA monoclonal antibody which comprises said CDRs and wherein said diagnostic agent comprises an imaging agent that is a radionuclide or a metal chelator complexed radionuclide, wherein said radionuclide is iodine, yttrium or technetium or is ^{131}I. Further, the light chain variable region of said humanized Class III, anti-CEA monoclonal antibody comprises a FR selected from SEQ ID NO:26, 27, 28 and 29 and combinations thereof; and the heavy chain variable region comprises a FR selected from SEQ ID NO:30, 31, 33, 36, 37 and 39 and combinations thereof, or FRL1 comprises SEQ ID NO:26, FRL2 comprises SEQ ID NO:27, FRL3 comprises SEQ ID NO:28, FRL4 comprises SEQ ID NO:29, FRH1 comprises SEQ ID NO:30 or 31, FRH2 comprises SEQ ID NO:33, FRH3 comprises SEQ ID NO:36 or 37 and FRH4 comprises SEQ ID NO:39 and wherein C may be in the sulfhydryl or disulfide form.

Claims 14-18 and 20 of U.S. Patent 6,676,924 are drawn to a method for diagnosing a patient comprising administering a conjugate comprising a humanized Class III, anti-CEA monoclonal antibody or fragment thereof bound to a diagnostic agent wherein the humanized Class III, anti-CEA monoclonal antibody or fragment thereof wherein the light chain variable region comprises CDRL1 comprising SEQ ID NO:20, CDRL2 comprising SEQ ID NO:21, and CDRL3 comprising SEQ ID NO:22 and the heavy chain variable region comprises CDRH1 comprising SEQ ID NO:23, CDRH2 comprising SEQ ID NO:24 and CDRH3 comprising SEQ ID NO:25 and each of the FR of the light and heavy chains are from a human antibody, wherein said humanized

monoclonal antibody retains the binding specificity of said parental murine Class III, anti-CEA monoclonal antibody and wherein said diagnostic agent comprises an imaging agent that is a radionuclide or a metal chelator complexed radionuclide, wherein said radionuclide is iodine, yttrium or technetium or is ^{131}I. Further, the light chain variable region of said humanized Class III, anti-CEA monoclonal antibody comprises a FRL1 comprising SEQ ID NO:26, FRL2 comprising SEQ ID NO:27, FRL3 comprising SEQ ID NO:28, FRL4 comprising SEQ ID NO:29, FRH1 comprising SEQ ID NO:30 or 31, FRH2 comprising SEQ ID NO:33, FRH3 comprising SEQ ID NO:36 or 37 and FRH4 comprising SEQ ID NO:39 and wherein C may be in the sulfhydryl or disulfide form.

Thus, diagnostic method of claims 14-18 and 20 of U.S. Patent 6,676,924, is a species that reads upon claims 30-42 of the instant application which are drawn to a diagnostic method comprising a genus of humanized Class III, anti-CEA monoclonal antibodies and fragments thereof that comprise a CDR selected from SEQ ID Nos:20-25, meaning that the instant claims are inclusive to using a humanized Class III, anti-CEA monoclonal antibody and fragment thereof that comprises all of the CDR sequences of SEQ ID Nos:20-25, i.e., species anticipates the genus. Applicant is reminded that the transitional term "comprising" is inclusive or open-ended and does not exclude additional, unrecited elements or method steps. See MPEP 2111.03. Additionally, because being unreactive with meconium antigen by enzyme immunoassay is one property of a Class III, anti-CEA monoclonal antibody, and the humanized antibody of claims 14-18 and 20 of U.S. Patent 6,676,924 is a Class III, anti-CEA

monoclonal antibody it necessarily is unreactive with meconium antigen by enzyme immunoassay (see col. 6, lines 1-5). Products of identical chemical composition cannot have mutually exclusive properties. A chemical composition and its properties are inseparable. In re Spada 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01.

18. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure:

Sharkey R. M. et al. Cancer, 71(6):2082-2096, March 15, 1993.

Sharkey R. M. et al. Cancer Research, 50(3 Suppl.):828s-834s, February 1, 1990.

Blumenthal R. D. et al. Cancer research, 52(21) :6036-6044, November 1, 1992.

Conclusion

19. No claim is allowed.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832. The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
David J. Blanchard
571-272-0827